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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07B 53/00, C07C 29/143, 35/27, 45/30, 49/697

A1

(11) International Publication Number: **WO 95/15299**

(43) International Publication Date: 8 June 1995 (08.06.95)

(21) International Application Number: PCT/IB94/00263

(22) International Filing Date: 2 September 1994 (02.09.94)

(30) Priority Data:
08/159,156 30 November 1993 (30.11.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/159,156 (CON)
Filed on 30 November 1993 (30.11.93)

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(81) Designated States: CA, FI, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: PROCESS FOR PREPARING A CHIRAL TETRALONE

(57) Abstract

A process for preparing the chiral (4S)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone is disclosed wherein racemic 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone is asymmetrically reduced by contacting the racemic tetralone with an asymmetric reagent to produce a mixture of cis and trans alcohols, separating the cis from the trans alcohols, and oxidizing the (4S) enantiomer of the resulting cis and trans alcohols. Also disclosed are novel intermediates used in the synthesis of the above chiral tetralone.

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PROCESS FOR PREPARING A CHIRAL TETRALONE

Background of the Invention

The present invention relates to a novel process for asymmetrically reducing racemic 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (hereinafter also referred to as "the tetralone" or "the racemic tetralone") and for preparing chiral (4S)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (hereinafter also referred to as "the chiral tetralone"), which has utility as an intermediate in the production of pure cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine (sertraline). Sertraline is a known antidepressant agent. This invention also relates to novel intermediates in the synthesis of chiral tetralone.

Several documents relate to the synthesis of pure racemic N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine starting with 3,4-dichlorobenzophenone and proceeding via racemic (±)-4-(3,4-dichlorophenyl)-4-butanoic acid and then to (±)-4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone. See, e.g., U.S. Patent Nos. 4,536,518 (August 20, 1985); 4,556,676 (December 3, 1985); 4,777,288 (October 11, 1988); and 4,839,104 (June 13, 1989); and Journal of Medicinal Chemistry, Vol. 27, No. 11, p. 1508 (1984).

Tetrahedron, Vol. 48, No. 47, pp. 10239-10248 (1992) relates to a process for preparing the (4S)-enantiomer of 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone comprising reducing the 4-ketobutanoic acid ester with a carbonyl reducing agent, as outlined in E. J. Corey et al., Journal of Organic Chemistry, Vol. 53, p. 2861 (1988), to ultimately afford chiral tetralone.

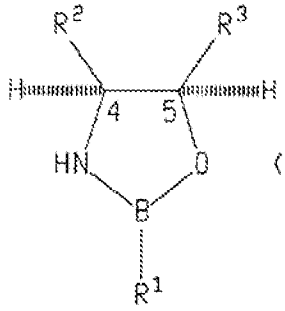
Other asymmetric methods of synthesis have been employed in the art, such as those described by W. M. Whitesides et al., Journal of the American Chemical Society, Vol. 91, No. 17, p. 4871 (1969); K. Mori et al., Synthesis, p. 752 (1982); B. H. Lipshutz et al., Journal of Organic Chemistry, Vol. 49, p. 3928 (1984); B. H. Lipshutz et al., Journal of the American Chemical Society, Vol. 104, p. 4696 (1982); G. M. Whitesides et al., Journal of the American Chemical Society, Vol. 91, No. 17 (1969); C. R. Johnson et al., Journal of the American Chemical Society, Vol. 95, No. 23, p. 7783 (1973); B. H. Lipshutz et al., Tetrahedron, Vol. 40, No. 24, p. 5005 (1984); and C. R. Johnson et al., Journal of the American Chemical Society, Vol. 95, No. 23, p. 7777 (1973).

All of the documents cited herein, including the foregoing, are incorporated herein in their entireties.

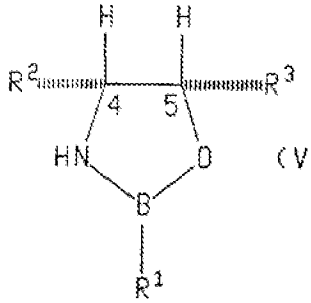
Summary of the Invention

Broadly, the present invention relates to a process for asymmetrically reducing racemic 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone comprising reacting the racemic 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone with an asymmetric ketone reducing agent. The asymmetric ketone reducing agent is preferably a catalytic chiral oxazaborolidine compound.

Preferred chiral oxazaborolidine compounds have the formula:



(V) or



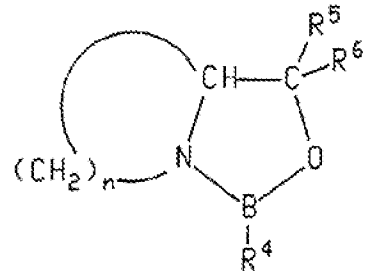
(Va)

wherein:

R^1 is hydrogen, (C_1-C_8) alkyl, benzyl, phenyl or phenyl substituted with up to three substituents independently selected from (C_1-C_8)alkyl, (C_1-C_8)alkoxy and halo; and

R^2 and R^3 are syn and the same and are each phenyl or phenyl substituted with up to three substituents independently selected from (C_1-C_8)alkyl, (C_1-C_8)alkoxy and halo.

Other preferred chiral oxazaborolidine compounds have the formula:



(VI)

wherein:

R^4 is hydrogen, lower alkyl or aralkyl;

n is 2, 3, or 4, such that the group $(CH_2)_n$ forms, together with the oxazaborolidine nitrogen and adjacent carbon, a 4-, 5- or 6-membered ring; and

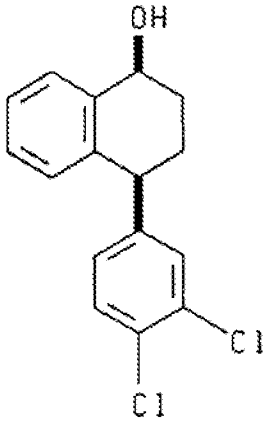
R^5 and R^6 are phenyl.

Another preferred asymmetric ketone reducing agent comprises either enantiomer of the compound having the formula:

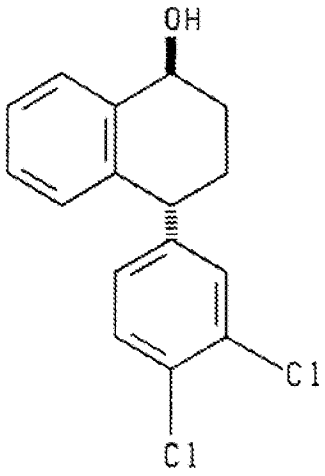
$$Ipc_2BX$$

wherein Ipc is isopinocampheyl, B is boron and X is halo.

The reduction of the racemic tetralone, depending on the asymmetric ketone reducing agent chosen, will yield either cis and trans alcohols having the following formulae:

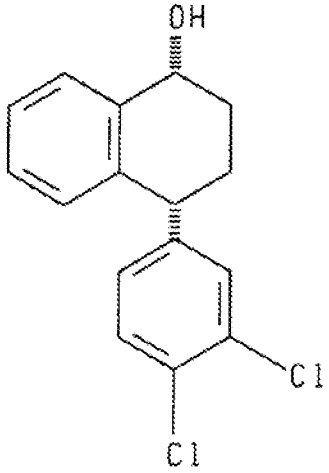


and



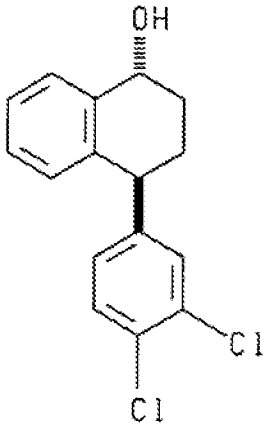
(I) (III)

or cis and trans alcohols having the following formulae:



(IV)

and

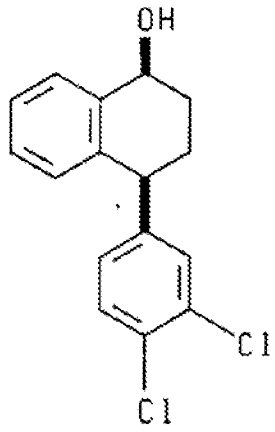


(II)

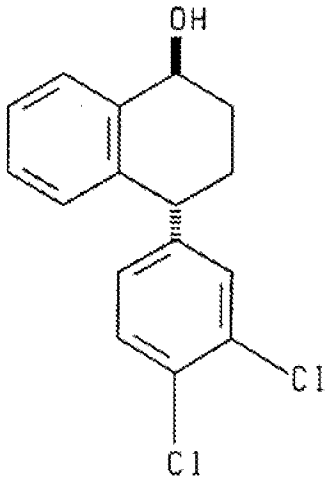
The enantiomer of the asymmetric reducing agent determines whether (I) and (III) or (II) and (IV) is produced.

The present invention also relates to each of the two reduction processes described above (i.e., that which produces compounds (I) and (III) and that which produces compounds (II) and (IV)), further comprising separating, respectively, the cis alcohol (I) from the trans alcohol (III) or the cis alcohol (IV) from the trans alcohol (II) and oxidizing, respectively, the resulting cis alcohol (I) or trans alcohol (II) to produce chiral tetralone.

The present invention also relates to a process comprising reacting racemic tetralone with an asymmetric ketone reducing agent to produce compounds having the formulae:



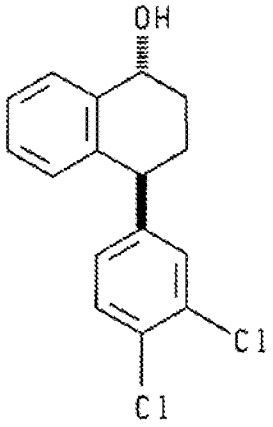
and



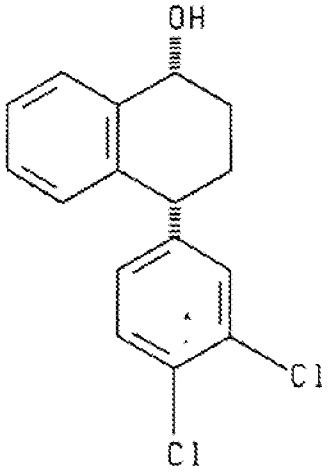
;

(I) (III)

or compounds having the formulae:



and

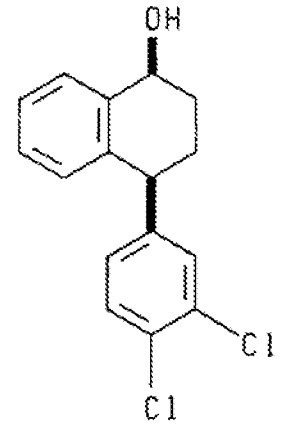


;

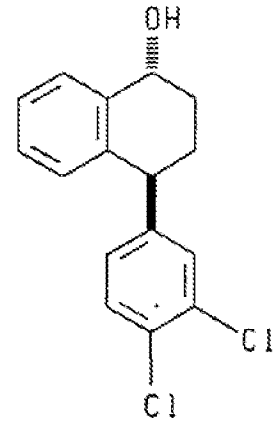
(II) (IV)

said process further comprising the steps of oxidizing the compounds having, respectively, formula (III) or (IV) to produce the 4(R) enantiomer of the tetralone ((4R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone), and contacting the resulting 4(R) tetralone with a base to produce racemic tetralone.

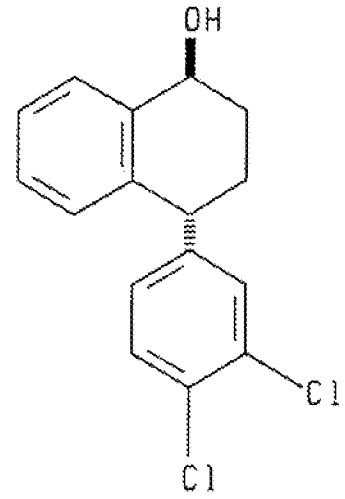
The present invention also relates to compounds having the following formulae:



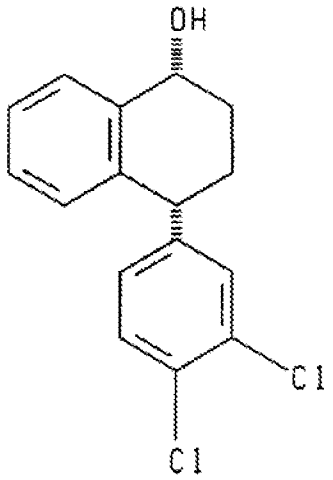
(I) ;



(II) ;



(III) ; and



(IV)

The term "halo", as used herein, unless otherwise indicated, includes chloro, fluoro, bromo and iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined as above.

The term "aralkyl", as used herein, includes aryl groups, wherein "aryl" is defined as below, terminating in an alkyl group, as defined above, which is the point of attachment.

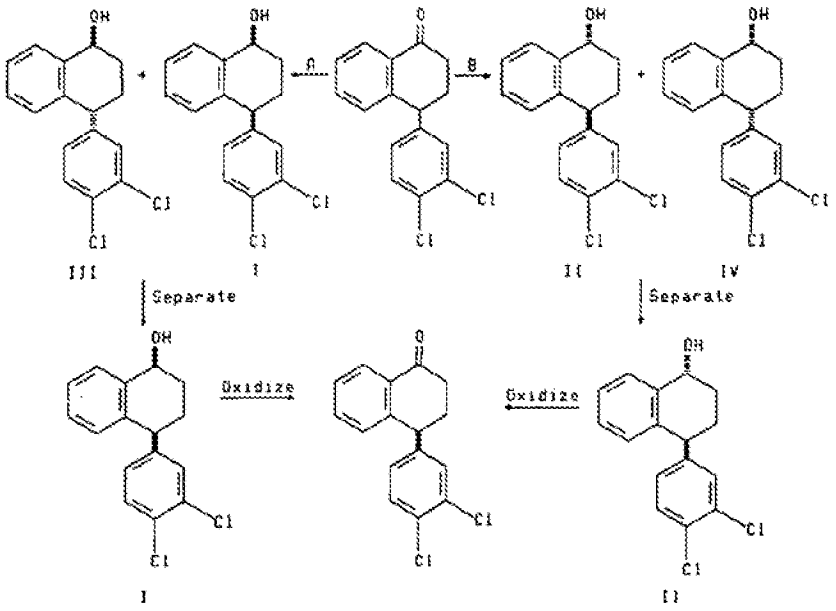
The term "aryl", as used herein, means mononuclear aromatic hydrocarbon groups such as phenyl, which can be unsubstituted or substituted in one or more positions, and polynuclear aryl groups such as naphthyl, anthryl, phenanthryl, and so forth, which can be unsubstituted or substituted with one or more groups.

The term "one or more substituents", as used herein, includes from one to the maximum number of substituents possible based on the number of available bonding sites.

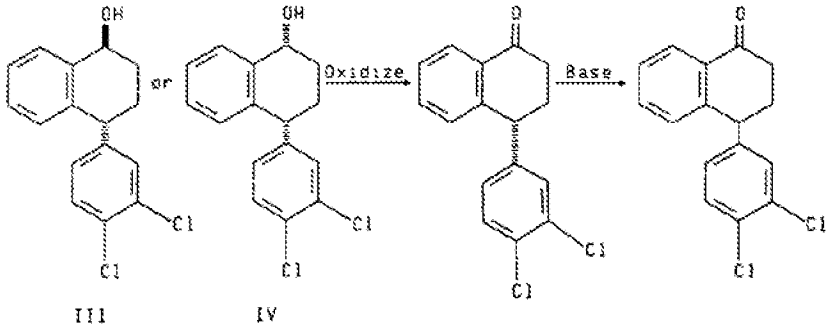
Detailed Description of the Invention

The processes of this invention for preparing the chiral tetralone (4S)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone are depicted in the following reaction schemes:

Scheme 1



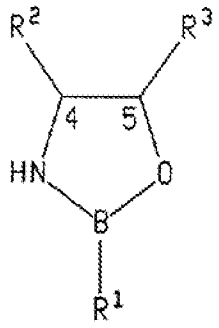
Scheme 2



Referring to Scheme 1, racemic 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (tetralone) is asymmetrically reduced by reacting the racemic tetralone with an asymmetric reagent (A) or (B), wherein (A) and (B) are enantiomers. Reduction of racemic tetralone with enantiomer A yields compounds of formulae I and III. Reduction of racemic tetralone with enantiomer B yields compounds of formulae II and IV.

The reduction is performed in a suitable solvent such as tetrahydrofuran, toluene, or an alternative etherial solvent. The reduction is performed at a temperature of from about -20°C to about 50°C, preferably from 20°C to 25°C. The ratio of racemic tetralone to asymmetric reagent is from about 1.0:0.025 to about 1.0:1.5. When the asymmetric reagent is a compound of formula (V), (Va) or (VI), then the ratio of racemic tetralone to asymmetric reagent is preferably from about 1.0:0.025 to about 1.0:0.1. When the asymmetric reagent is a compound of formula Ipc_2BX, then the ratio of racemic tetralone to asymmetric reagent is preferably from about 1.0:1.0 to about 1.0:1.5. The asymmetric reduction of racemic tetralone produces a mixture of cis and trans alcohols of the formulae (I) and (III) or of the formulae II and IV depending upon the chirality of the asymmetric reagent employed. The cis alcohol (I) can be separated from the trans alcohol (III) by methods known in the art, such as chromatography. Similarly, the trans alcohol II can be separated from the cis alcohol IV by methods known in the art. In each case, the desired product possesses the chirality desired for sertraline. The (4S) tetralone can be prepared by Jones oxidation, Swern oxidation, Manganese dioxide, pyridium chlorochromate, and pyridium dichromate of the resulting cis alcohol (I) and trans alcohol (II).

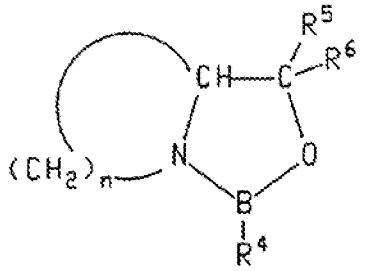
Examples of suitable asymmetric reducing reagents include chiral oxazaborolidine compounds of the formula:



(V)

wherein R^1 is hydrogen, $(C_1\text{-}C_8)$alkyl, benzyl, phenyl or phenyl substituted with up to three substituents independently selected from $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$alkoxy or halo; and R^2 and R^3 are syn and the same and are each phenyl or phenyl substituted with up to three substituents independently selected from $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$alkoxy or halo groups such as chloro or fluoro. A preferred number of substituents is zero. A preferred group of such compounds is the group of compounds wherein R^1, R^2 and R^3 are all unsubstituted phenyl. Especially preferred is the compound wherein R^2 and R^3 are each unsubstituted phenyl and R^1 is methyl. Also, especially preferred is the compound wherein R^2 and R^3 are each phenyl and R^1 is hydrogen.

Suitable asymmetric reagents also include a chiral 1,3,2-oxazaborolidine of the formula:



(VI)

in which: R^4 is hydrogen, lower alkyl or aralkyl; n is 2, 3, or 4, such that the group $(CH_2)_n$ forms, together with the oxazaborolidine nitrogen and adjacent carbon, a 4-, 5- or 6-membered ring; and R^5 and R^6 are phenyl. Aralkyl is as defined above. Preferred alkyl groups of the aralkyl are CH_2. Preferred aralkyl groups are phenylalkyl groups.

Suitable asymmetric reagents also include a haloborane represented by the formula: Ipc_2BX, wherein Ipc is isopinocampheyl, B is boron and X is halo.

Additional suitable asymmetric reagents are disclosed in U.S. Patent No. 5,189,177 issued February 23, 1993; U.S. Patent No. 4,943,635 issued July 24, 1990; U.S. Patent No. 4,772,752 issued September 20, 1988; U.S. Patent Application Serial No. 08/061,895 filed May 14, 1993; International Patent Application PCT/US93/00687, filed February 1, 1993; International Patent Application PCT/US92/05434, filed July 1, 1992; and International Patent Application PCT/US92/05433, filed July 1, 1992.

Referring to Scheme 2, the process for making (4S)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone may optionally contain one or more additional steps wherein alcohols (III) and/or (IV) are recycled. In this process, the alcohols (III) and/or

(IV) are oxidized to produce 4(R) enantiomer of the tetralone, which is then reacted with a base to produce the racemic tetralone. The oxidation can be done by methods known to those skilled in the art. The racemization reaction is performed at a temperature of from about 0°C to about 100°C, preferably 25°C to 65°C. The 4(R) enantiomer of the tetralone is reacted with a base at a temperature of from about 25°C to about 65°C, preferably 50°C to 80°C. Suitable bases for this reaction include potassium t-butoxide, sodium hydroxide, sodium methoxide, and potassium hydroxide. A preferred base is potassium t-butoxide.

The (4S)-4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone final product afforded by the process of this invention is a valuable intermediate that can be used to synthesize the antidepressant agent known as sertraline or cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine by methods disclosed in the previously discussed prior art. More specifically, (4S)-4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone is first converted to (4S)-N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidine]methanamine and then finally to the desired cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine by the known methods of the prior art process, as earlier described in U.S. Patent No. 4,536,518 (August 20, 1985). In the present instance, the optically-active ketone, viz., (4S)-4-(3,4-dichlorophenyl)-1(2H)-naphthalenone, is first reductively aminated to give chiral cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine and the latter product is then separated by chromatographic means to ultimately yield the desired final medicinal product which is sertraline.

The preparation of other compounds of the present invention not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

In each of the reactions discussed or illustrated in Schemes 1 or 2 above, pressure is not critical unless otherwise indicated. Pressures from about 0.9 atmospheres to about 2 atmospheres are generally acceptable and ambient pressure, i.e., about 1 atmosphere, is preferred as a matter of convenience.

The activity, methods for testing activities, dosages, dosage forms, methods of administration and background information concerning sertraline are set forth in U.S. Patent Nos. 4,536,518 (August 20, 1985), 4,777,288 (October 11, 1988), and 4,839,104

(June 13, 1989), and the Journal of Medicinal Chemistry, Vol. 27, No. 11, p. 1508 (1984).

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples.

EXAMPLE 1

(4S)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone

Borane methylsulfide complex (2M in THF, 6.0 mL, 12 mmol) was added all at once to a solution of (1S, 2R)-(+)-erythro-2-amino-1,2-diphenylethanol [J. Amer. Chem. Soc. 1216 (1951) also commercially available] (183 mg, 0.86 mmol) in THF (55 mL) under a nitrogen atmosphere. The solution was stirred for 18 hours. Racemic tetralone (5.0 g, 17 mmol) as a solution in THF was added over 1 hour, the reaction stirred 15 minutes after the addition was completed, cooled to 0°C and quenched with methanol. After stirring the quenched reaction for 18 hours the solvents were removed under vacuum, the contents dissolved in methylene chloride (100 mL), and washed sequentially with pH4 phosphate buffer (100 mL), water (100 mL), treated with magnesium sulfate, and solvent removed to afford a mixture of the cis and trans alcohols (5.01 g). Chromatography with ethyl acetate/hexanes provided the less polar cis alcohol. ^{1}H NMR δ ($CDCl_3$) 7.46 (dd, J=1Hz, J=7Hz, 1H), 7.41-7.07 (m, 4H), 6.98 (dd, J=2Hz, J=8Hz, 1H), 6.82 (d, J=7Hz, 1H), 4.86 (t, J=4Hz, 1H), 3.99 (t, J=8Hz, 1H), 2.18-1.87 (m, 5H). ^{13}C NMR δ 147.0, 138.9, 138.4, 132.4, 130.7, 130.4, 130.2, 129.8, 129.1, 128.3, 128.2, 127.1, 67.9, 45.1, 30.1, 28.2 and the more polar trans alcohol. ^{1}H NMR ($CDCl_3$) δ 7.54 (d, J=7Hz, 1H), 7.4-7.07 (m, 4H), 6.90-6.75 (m, 2H), 4.88 (t, J=5Hz, 1H), 4.13 (t, J=6Hz, 1H), 2.43-1.63 (m, 5H). The less polar cis alcohol 1 (160 mg, 0.546 mmol) was dissolved in methylene chloride (5 mL), treated with pyridium chlorochromate (220 mg, 1.023 mmol), and stirred for 2 hours at ambient temperature. Diethyl ether was added (25 mL), stirred 20 minutes, and the solvent decanted. The residual dark gum was washed with diethyl ether (2 X 15 mL), the organic layers combined, filtered through a pad of magnesium sulfate, and solvent removed under vacuum to afford a brown oil (170 mg). Chromatography on silica (5.1 g) eluting with methylene chloride provided the chiral tetralone as a clear oil (118 mg). This material was determined to be $\geq$ 95% ee by HPLC with a chiral support (Diacel Co. ChiralcelOD 4.6 mm X 25 cm, 10% isopropyl alcohol/hexane).

EXAMPLE 2

(4S)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone

(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone ("the tetralone") (5 g, 17 mmol),(S)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-c][1,3,2]oxazaborole[J. Org. Chem. 2861 (1988)] (238 mg, 0.859 mmol), and tetrahydrofuran (THF) (68 mL) were combined at ambient temperature in a flamed dried flask under a nitrogen atmosphere. Borane methylsulfide complex (2 M in THF, 4.56 mL) was added over 1 hour, 30 minutes later the reaction was quenched at 0°C with methanol (16.8 mL), and stirred for 18 hours. The solvents were removed under vacuum, the contents dissolved in methylene chloride (68 mL), and washed sequentially with pH4 phosphate buffer (68 mL), water (68 mL), treated with magnesium sulfate, and solvent removed to afford a mixture of the cis and trans alcohols (4.93 g). Chromatography with ethylacetate/hexanes provided the less polar cis alcohol αD=-52.27 (c=1.01, methylene chloride) and more polar trans alcohol αD=+37.79 (c=1.18, methylene chloride). The more polar trans alcohol 2 (160 mg, 0.546 mmol) was dissolved in methylene chloride (5 mL), treated with pyridium chlorochromate (220 mg, 1.023 mmol), and stirred for 2 hours at ambient temperature. Diethyl ether was added (25 mL), stirred 20 minutes, and the solvent decanted. The residual dark gum was washed with diethyl ether (2 X 15 mL), the organic layers combined, filtered through a pad of magnesium sulfate, and solvent removed under vacuum to afford a brown oil (162 mg). Chromatography on silica (5 g) eluting with 25% ethyl acetate/hexanes provided the chiral tetralone as a clear oil (139 mg) αD=+36.8 (c=1.11) which corresponds to a 56% ee.

EXAMPLE 3

(4S)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone

[(+)-ß-chlorodiisopinocampheylborane] (6.07 g, 18.97 mmol) was dissolved in THF (13.6 mL) under a nitrogen atmosphere, and cooled to -25°C. Tetralone (5 g, 17 mmol) was added as a solution in THF (13.6 mL), the contents allowed to warm to ambient temperature, and stirred 46 hours. The solvent was removed under vacuum, diethyl ether (65 mL) and ethanol amine (3.9 mL) were added, and the contents stirred for 18 hours. The precipitate was filtered off, washed with pentane (2 X 20 mL), and the solvent removed under vacuum from the filtrate to yield the crude product (4.98 g) which was chromatographed on silica with 25% ethyl acetate/hexanes to separate the cis and trans alcohols. The more polar trans alcohol 2 (175 mg, 0.579 mmol) was

dissolved in methylene chloride (5 mL) and treated with pyridium chlorochromate (192 mg) for 2 hours at ambient temperature. Diethyl ether was added (25 mL), stirred 15 minutes, and the solvents decanted. The residual black semisolid was washed with diethyl ether (2 X 10 mL), the organic phases combined, filtered through CELITE, and solvent removed under vacuum to yield the crude chiral tetralone. Chromatography on silica eluting with 25% ethyl acetate/hexanes afforded 165 mg of pure product $\alpha D = +30.94$ (c=1.28, acetone) which corresponds to 47% ee.

EXAMPLE 4

4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone

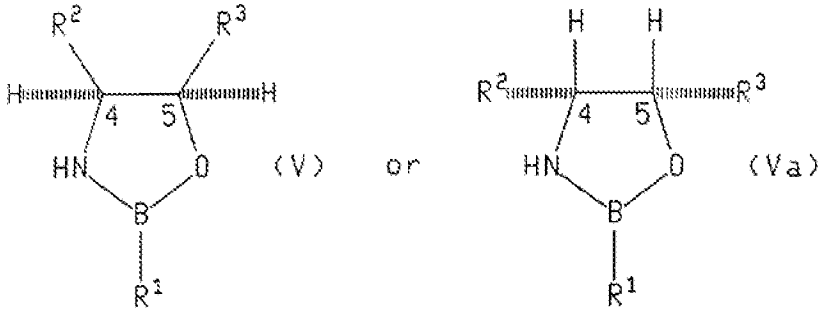
Pyridium chlorochromate oxidation of the trans alcohols 3 and 4 with the same procedure employed on alcohols 1 and 2 provided the chiral tetralone. Racemization of the chiral tetralone into racemic tetralone was achieved as follows. Potassium t-butoxide (90 mg, 0.80 mmol) was added to a solution of chiral tetralone (1.12 g, 3.84 mmol) in THF (4 mL). The solution was refluxed for 18 hours under nitrogen, cooled to ambient temperature, methylene chloride (10 mL) and aqueous hydrochloric acid (1N, 20 mL) added, and the phases separated. The organic phase was washed with water (10 mL), brine (10 mL), dried with magnesium sulfate, and solvent removed under vacuum to yield 1.1 g of the crude racemic tetralone. Recrystallization from methanol afforded 1.07 g (95%) of the racemic tetralone mp-104-5°C. Other base solvent combinations which effect racemization are methanol/sodium methoxide, methanol/sodium hydroxide, and methanol/potassium hydroxide.

CLAIMS

1. A process for asymmetrically reducing racemic 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone comprising reacting the racemic 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone with an asymmetric ketone reducing agent.

2. A process according to claim 1 wherein the asymmetric ketone reducing agent is a chiral catalytic oxazaborolidine compound.

3. A process according to claim 2 wherein the chiral oxazaborolidine compound has the formula:

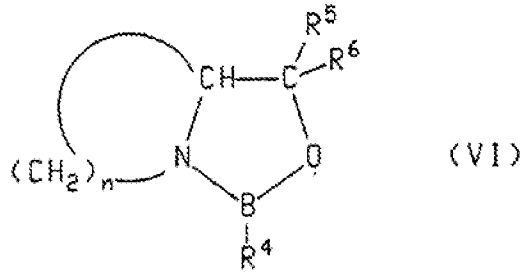


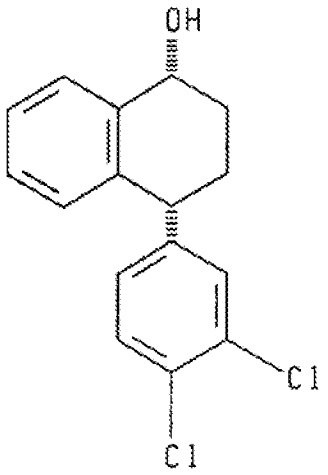
wherein:

R^1 is hydrogen, (C_1-C_8) alkyl, benzyl, phenyl or phenyl substituted with up to three substituents independently selected from (C_1-C_8)alkyl, (C_1-C_8)alkoxy and halo; and

R^2 and R^3 are syn and the same and are each phenyl or phenyl substituted with up to three substituents independently selected from (C_1-C_8)alkyl, (C_1-C_8)alkoxy and halo.

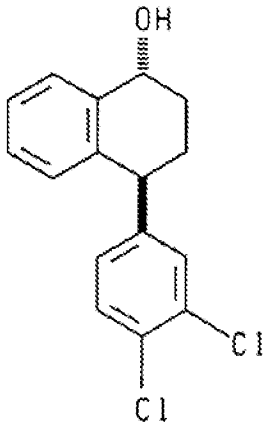
4. A process according to claim 2 wherein the chiral oxazaborolidine compound has the formula:





(IV)

and



(II)

8. A process according to claim 6 wherein said process further comprises the steps of separating the cis alcohol (I) from the trans alcohol (III) and oxidizing the the resulting cis alcohol (I) to produce chiral tetralone.

9. A process according to claim 7 wherein said process further comprises the steps of separating the cis alcohol (IV) from the trans alcohol (II) and oxidizing the the resulting trans alcohol (II) to produce chiral tetralone.

10. A process according to claim 1 wherein the reaction of racemic tetralone with an asymmetric ketone reducing agent yields compounds having the formulae:

wherein:

R^4 is hydrogen, lower alkyl or aralkyl;

n is 2, 3, or 4, such that the group $(CH_2)_n$ forms, together with the oxazaborolidine nitrogen and adjacent carbon, a 4-, 5- or 6-membered ring; and

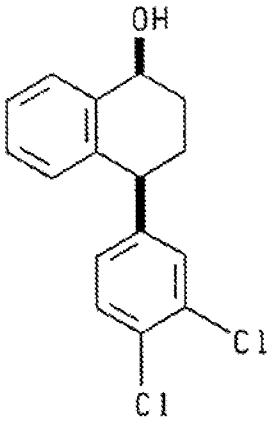
R^5 and R^6 are phenyl.

5. A process according to claim 1 wherein the asymmetric ketone reducing agent comprises either enantiomer of the compound having the formula:

$$Ipc_2BX$$

wherein Ipc is isopinocampheyl, B is boron and X is halo.

6. A process according to claim 1 wherein the reduction of the racemic tetralone yields cis and trans alcohols having the following formulae:



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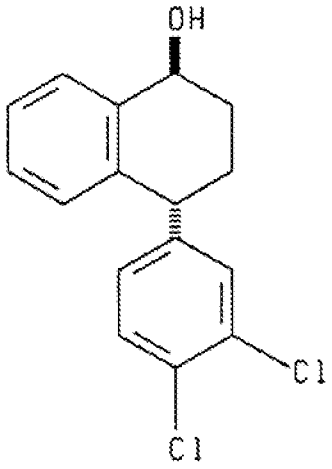
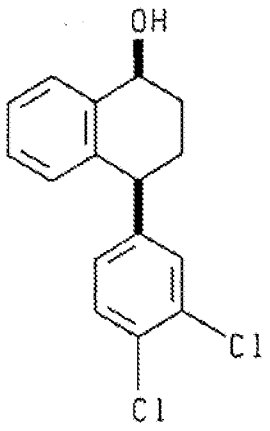


(I) (III)

7. A process according to claim 1 wherein the reduction of the racemic tetralone yields cis and trans alcohols having the following formulae:



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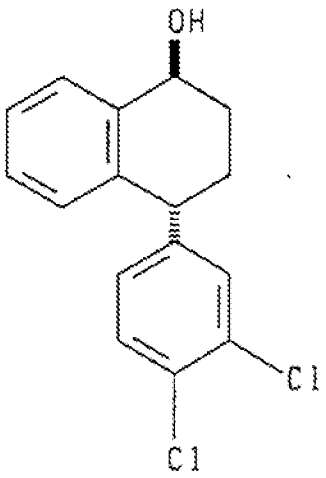
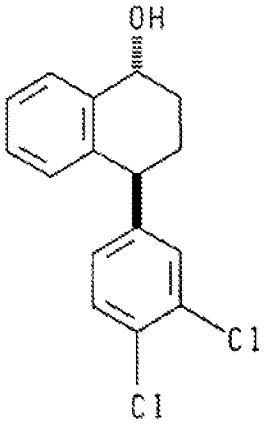


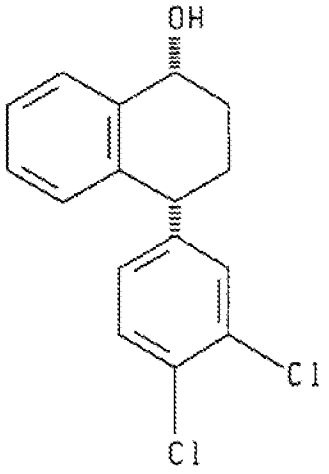
;

(I) (III)

or compounds having the formulae:



and



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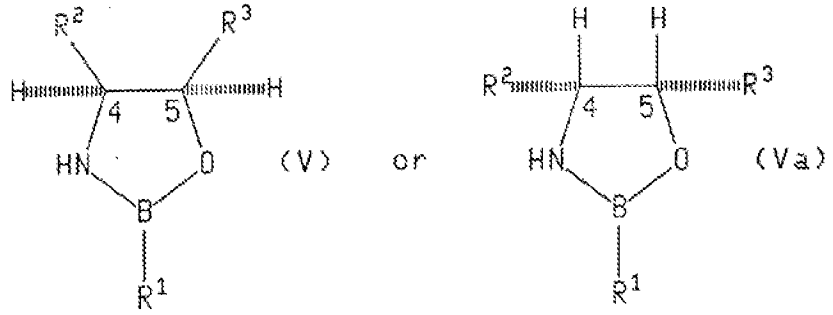
(II) (IV)

11. A process according to claim 10, further comprising the steps of oxidizing the compounds having formula (III) or (IV) to produce (4R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone, and contacting the resulting 4(R) tetralone with a base to produce racemic 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone.

12. A process according to claim 10 wherein said asymetric ketone reducing agent is a chiral oxazaborolidine having the formula:



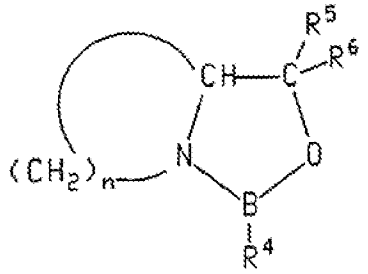
(V) or (Va)

wherein:

R^1 is hydrogen, (C_1-C_8) alkyl, benzyl, phenyl or phenyl substituted with up to three substituents independently selected from (C_1-C_8)alkyl, (C_1-C_8)alkoxy and halo; and

R^2 and R^3 are <u>syn</u> and the same and are each phenyl or phenyl substituted with up to three substituents independently selected from (C_1-C_8)alkyl, (C_1-C_8)alkoxy and halo.

13. A process according to claim 10 wherein said asymmetric ketone reducing agent is a chiral oxazaborolidine having the formula:



(VI)

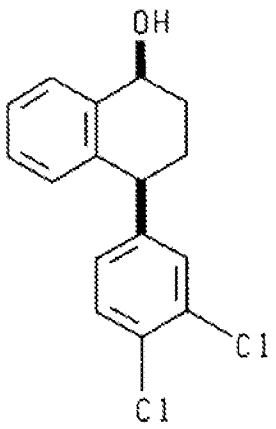
wherein:

R^4 is hydrogen, lower alkyl or aralkyl;

n is 2, 3, or 4, such that the group $(CH_2)_n$ forms, together with the oxazaborolidine nitrogen and adjacent carbon, a 4-, 5- or 6-membered ring; and

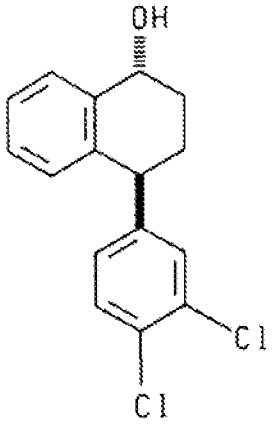
R^5 and R^6 are phenyl.

14. A compound of the formula:



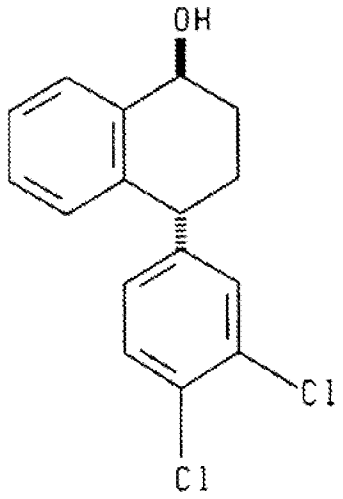
(I)

15. A compound of the formula:



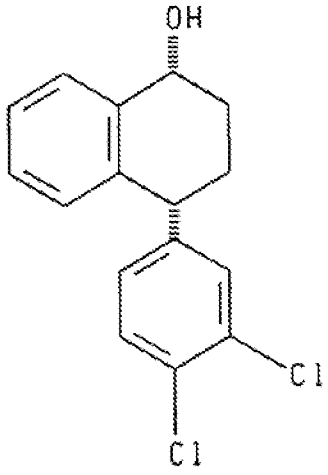
(II)

16. A compound of the formula:



(III)

17. A compound of the formula:



(IV)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/IB 94/00263

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07B53/00 C07C29/143 C07C35/27 C07C45/30 C07C49/697

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 23408 (PFIZER) 25 November 1993 see claims; examples 4,12	1-3
A	EP,A,0 305 180 (PRESIDENT AND FELLOWS OF HARVARD UNIVERSITY) 1 March 1989 see page 18, line 44; claims; example 2	1,2,4
A	US,A,4 772 752 (H BROWN) 20 September 1988 see claims; examples	1,5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 1994	-8. 11. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Heywood, C

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/IB 94/00263

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9323408	25-11-93	AU-B-	3593193	13-12-93
		HU-A-	65136	28-04-94
EP-A-0305180	01-03-89	US-A-	4943635	24-07-90
US-A-4772752	20-09-88	US-A-	4866181	12-09-89
		US-A-	5043479	27-08-91